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ORIGINAL ARTICLE

Exploring the active constituents of *Oroxylum indicum* in intervention of novel coronavirus (COVID-19) based on molecular docking method

Sapan Shah[1] · Dinesh Chaple[1] · Sumit Arora[2] · Subhash Yende[3] · Keshav Moharir[4] · Govind Lohiya[4]

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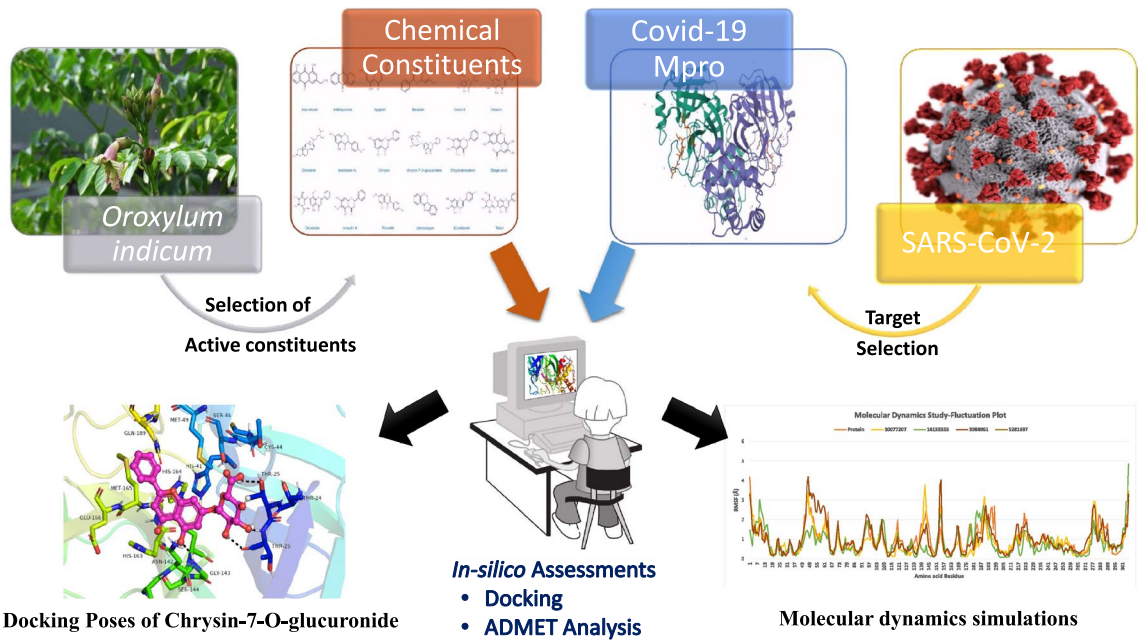
Abstract

The severe acute respiratory syndrome COVID-19 declared a global pandemic by WHO has become the present wellbeing worry to the whole world. There is an emergent need to search for possible medications. We report in this study a molecular docking study of eighteen *Oroxylum indicum* molecules with the main protease (M^{pro}) responsible for the replication of SARS-CoV-2 virus. The outcome of their molecular simulation and ADMET properties reveal four potential inhibitors of the enzyme (Baicalein-7-*O*-diglucoside, Chrysin-7-*O*-glucuronide, Oroxindin and Scutellarein) with preference of ligand Chrysin-7-*O*-glucuronide that has the second highest binding energy (− 8.6 kcal/mol) and fully obeys the Lipinski's rule of five.

Graphical abstract



Keywords COVID-19 · *Oroxylum indicum* · Molecular docking · Molecular dynamics · ADMET study

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✉ Sapan Shah
shah.sapan@rediffmail.com

Extended author information available on the last page of the article

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Abbreviations

AMES	*Salmonella typhimurium* Reverse mutation assay
WHO	World health organization
ADMET	Absorption, distribution, metabolism, excretion and toxicological
RNA	Ribonucleic acid
SDF	Spatial data file
NCBI	National Center for Biotechnology Information
UFF	Universal force field
SMILES	Simplified Molecular Input Line Entry System
hERG	Human ether-a-go-go-related gene
LOAEL	Lowest-observed-adverse-effect level
LD	Lethal dose
ATPase	Adenosine triphosphatase
DPPH	2,2-Diphenyl-1-picrylhydrazyl
ABTS	2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid
CAA	Cellular antioxidant activity
DENV	Dengue virus
QSAR	Quantitative structure activity relationship
CAESAR	Computer assisted evaluation of industrial chemical substances according to regulation
CoMPARA	Collaborative modeling project for androgen receptor activity
IRFMN	Estrogen receptor relative binding affinity model
NRMEA	Nuclear receptor-mediated endocrine activity model
ADI	Applicability domain index
SMILES	Simplified molecular-input line-entry system

1 Introduction

Corona viruses are enveloped and single-stranded ribonucleic acid (RNA) viruses which can infect humans as well as animal species (Wu et al. 2020a). These viruses are categorized into four genera as, α-corona virus (α-COV), β-corona virus (β-COV), δ-corona virus (δ-COV) and γ—corona virus (γ-COV). Till now, six human corona viruses are known; (CoV)—HCoV-NL63, HCoV-HKU1, HCoV-229E, HCoVOC43, Severe Acute Respiratory Syndrome Corona virus (SARS-CoV) and Middle East Respiratory Syndrome Corona virus (MERS-CoV). SARS-CoV and MERS-CoV have been reported to cause severe respiratory symptom and large number of deaths in past few years across globe (Wang et al. 2020). As on 06 November, 2020, the WHO has reported 48,534,508 confirmed cases and 1,231,017 death cases worldwide (WHO 2020) https://covid19.who.int/. Structural and non-structural proteins of SARS-CoV-2 have been proposed as potential drug targets. Various active targets of SARS-CoV-2 includes 3-chymotrypsin—like protease (3CLpro), papain like protease (PL^{pro}), RNA-dependent RNA polymerase, spike (S) proteins and human Angiotensin-converting enzyme (ACE) 2 (Wu et al. 2020b). Main protease (M^{pro}) or $3CL^{Pro}$ of corona virus is conserved among the corona viruses and it is mainly responsible for the viral replication. The mediation of nonstructural viral proteins and maturation by main protease makes M^{pro} a very attractive target for the development of anti-corona virus drugs (Vlachakis et al. 2020).

Currently, no recognized antiviral therapies or preventive vaccines are available for this pandemic disease. Antimalarial drugs like Chloroquine, Hydroxychloroquine sulfate and the antiviral drugs such as Remdesivir, Lopinavir/Ritonavir, Favipiravir were found to be efficacious in the treatment of patients infected with this virus and is a possible therapeutic option for COVID-19 (Philippe, Rolain Jean-Marc 2020; Zhang and Xie 2020). Now a day, plant extracts and isolated phytoconstituents are broadly used to evaluate their in vitro antiviral activities. The natural products such as conventional herbal medicines and phytochemicals are the rich sources of potential antiviral drugs (Liu and Du 2012). Some of the medicinal plants reported for its antiviral potential against notable viral pathogens include *Azadirachta indica, Artemisia annua, Pyrrosia lingua, Terminalia chebula, Piper longum*, etc. (Parida et al. 2002; Lin et al. 2014).

Oroxylum indicum (family: Bignoniaceae) commonly known as Shyonaka and Indian Trumpet tree due to resemblance of its flower to trumpet (Kirtikar and Basu 2001). It is an imperative herb in Ayurvedic medicine and has been used as an ingredient of polyherbal formulations like Dasamularistha, Amartarista, Dantyadyarista, Narayantaila, Dhanawantaraghrita, Brahmarasayan and Chyavanaprash. Pharmacologically, it has been found to possess antimicrobial, antidiabetic, antihyperlipidemic, hepatoprotective, analgesic and anti-inflammatory, anticarcinogenic, immunomodulatory, nephroprotective, antitussive cardioprotective, antiallergic, antibronchitic, antirheumatic activities (Ahad et al. 2012). Flavonoids, alkaloids, glycosides, essential oils and phenolic compounds has been reported as an important phytoconstituents (Lawania et al. 2010). Flavonoids such as baicalein, baicalin, chrysin, oroxylin-A, scutellarin, acacetin, hispidulin, isorhamnetin, and Isoquercetin, quercetin-3-o-α-L-arabinopyranoside,

1-(2-hydroxyethyl) cyclohexane-1,4-diol, apigenin, 2,5-dihydroxy-6,7-dimethoxy flavones, 3,7,3′,5′-tetramethoxy-4′-hydroxyflavone, pterocarpans, etc., has been isolated previously (Ahad et al. 2012; Deka et al. 2013). Other chemical constituents such as Prunetin, β-Sitosterol, Stigmasterol glucoside, Ellagic acid, Triterpene Carboxylic acid, Ursolic Acid, Lupeol, p-Coumaric Acid, Napthquinones, Anthraquinone, Phenylethanoid glycosides, and Cyclohexylethanoids are also extracted from this plant (Yan et al. 2011; Dinda et al. 2015).

Drug discovery is a time consuming and challenging process. Moreover, to screen out large number phytoconstituents from herbs with antiviral activity against corona virus will be a challenge in very short period. Considering the consequence of increase in the number of active cases and death cases in current time and deficient effective treatment, computer aided drug design is an important approach to be preferred. In silico process of drug design will minimize the time and expenditure require in the drug research (Kiran et al. 2020).

Literature suggest that there is no study reported for *Oroxylum indicum* as antiviral drug although owning reach source of constituents, makes it possible herbal contender to interfere with the corona virus life cycle. Hence, the aim of the current study is to identify the potential antiviral phytoconstituents from *Oroxylum indicum* against target main protease (PDB ID: 6LU7) using molecular simulation study.

2 Materials and methods

2.1 Protein preparation

In silico analysis of phytoconstituents of *Oroxylum indicum* was performed on 2.16 Å crystal structure of COVID-19 M^{pro}: main protease in complex with an inhibitor N3 (PDB ID: 6LU7) also a key CoV enzyme which plays a pivotal role in mediating viral replication and transcription, making it an attractive drug target for this virus (Isah 2019), which was retrieved from protein data bank (https://www.rcsb.org). The 6LU7 protein contains two chains, A and B, which form a homodimer. Chain A was used for macromolecule preparation (Fig S1).

The protein was visualised using PyMol (http://www.pymol.org) and unwanted chain residues, bound ligand N3, water molecules were removed. Additionally to prepare protein, charges added and minimized the energy of the protein using Autodock Vina in PyRx open source software and subsequently converting it to pdbqt format.

2.2 Ligand preparations

For this investigation, chemical structures of chemical constituents of *Oroxylum indicum* were retrieved in a SDF format from chemical database PubChem available on NCBI

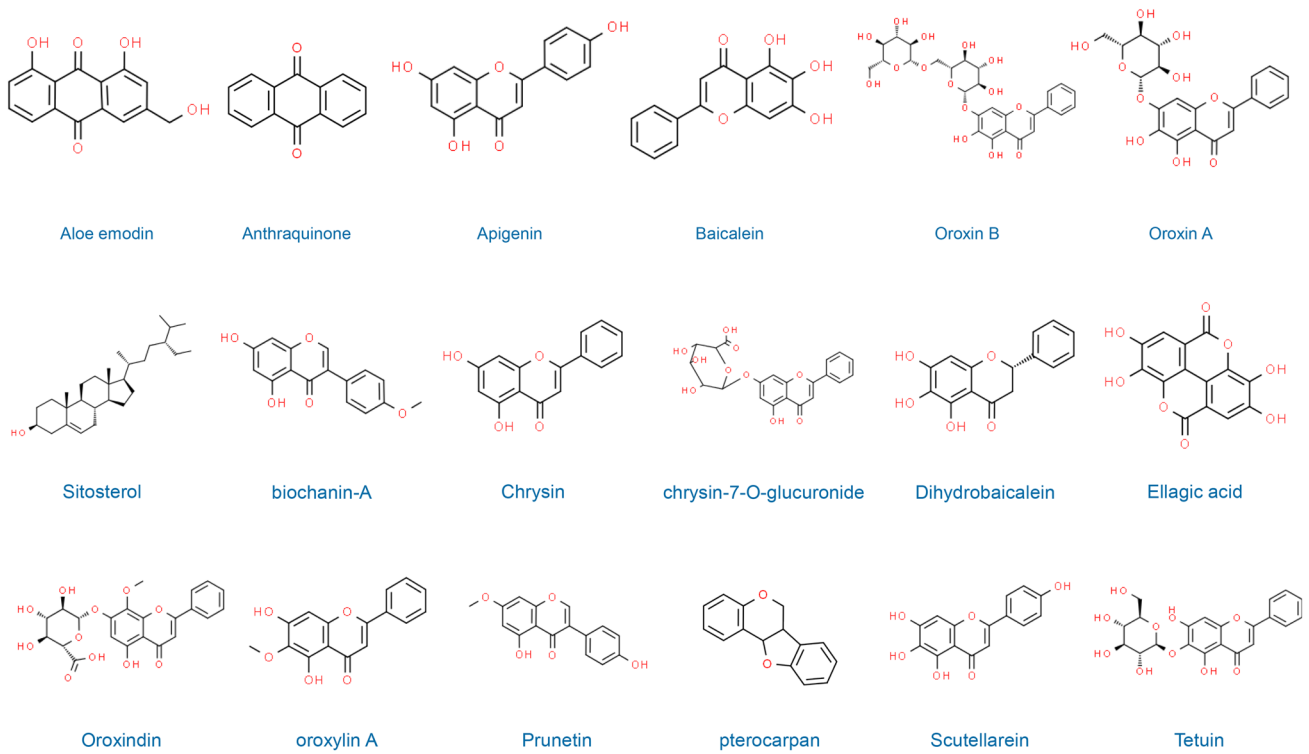

Fig. 1 Chemical structure of all selected ligand molecules in docking studies

website (https://pubchem.ncbi.nlm.nih.gov/). The ligand N3 (*N*-[(5-methylisoxazol-3yl) carbonyl] alanyl-l-valyl-*n*~1~-((1R, 2Z)-4-(benzyloxy)-4-oxo-1-{[(3R)-2-oxopyrrolidin-3-yl] methyl} but-2-enyl)-l-leucinamide) was obtained from database of chemspider. CSID:4883311, http://www.chemspider.com/ChemicalStructure.4883311.html (accessed 04:56, May 12, 2020). Using OpenBabel control all ligands were loaded into the PyRx virtual screening software. The OpenBabel software converts the SDF files of the ligands to PDB format (O'Boyle et al. 2011). Further, the ligands are prepared by detecting the torsion root, correcting the torsion angles, assigning charges, optimizing using UFF (Universal force field) (Jaillet et al. 2017) and finally converting them to pdbqt format to generate 3D atomic coordinates of the molecules. The chemical structures of all the ligands is depicted in Fig. 1.

2.3 Receptor grid generation and molecular docking

A primary objective in molecular docking was the ability to estimate the scoring function and to evaluate interactions between a protein and small molecules based on the geometry in order to predict the binding affinity and activity of the ligand molecule (Verdonk et al. 2003; Leach et al. 2006). In this study, docking was performed using Autodock Vina in PyRx virtual screening open source software (Leach et al. 2006). The protein and ligand molecules to be docked are selected under the Vina wizard control. A grid appears over the protein structure. The grid size can be adjusted according to the active site residues that are selected and Autodock Vina is run. A grid box with the size $32.803 \times 27.870 \times 26.639$ with coordinates (x,y,z) of -9.8336, 11.1638, 69.5594 having the grid spacing of 0.375 Å was used. The docking Lamarckian Genetic Algorithm (LGA) was allowed to produce 10 docked positions for each ligand (Fuhrmann et al. 2010). The docking results can be viewed under 'analyse results' tab. Although, the final results were analyzed and visualized on the basis of docking scores using Discovery Studio 2020 Client (Biovia 2016) and PyMol software's (DeLano 2002).

2.4 Molecular dynamics (MD) studies

To perform molecular dynamics simulations, CABS Flex 2.0 server were used. It is based on coarse-grained simulations of protein motion (Kurcinski et al. 2019) for 50 cycles, 50 trajectory frames for 10 ns with some additional distance restraints with a global weight of 1.0, built with Poisson-Boltzmann/Generalized Born (PB/GB) molecular mechanics the solvent probe radius was set as 1.4 Å, minimum atomic radius 1 Å, salt radius 2 Å, ionic strength 0.15, temperature of simulation 1.4, in order to analyze the conformational stability of the receptor-ligand complex system.

2.5 ADME and toxicity studies

The ligands were further screened for Lipinski rule of five by following certain criteria such as molecular weight ≤ 500, log$P \leq 5$, hydrogen bond donor ≤ 5, hydrogen bond acceptor ≤ 10 and topological polar surface area ≤ 500. During drug development, safety is always the most important issue, therefor Toxicology prediction of small molecules is important to predict amount of tolerability of the small molecule before being ingested into the human and animal models. Two main approaches for assessment of phytoconstituents toxicity, webserver based and quantitative structure activity relationship.

pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) is an online server database in which the small molecule can be analyzed for calculating pharmacokinetic and toxicological properties by uploading the SMILES of molecules. We can obtain the details of toxicological effects in the fields of AMES Toxicity, human maximum tolerance dose, hERG-I inhibitor, hERG-II inhibitor, LD50, LOAEL, Hepatotoxicity, Skin Toxicity, *T. pyriformis* toxicity and Minnow toxicity(Pires et al. 2015).

VEGA-QSAR ((http://www.vega-qsar.eu/) is integrating In silico QSAR models and read-across method for a number of toxicological data outcomes(Rogiers et al. 2020). The molecules can be analyzed for calculating toxicological properties by either inserting SMILES notations or uploading SDF files and then selecting toxicological models for generating numerous information about structure related effects. The results also show structural alerts in chemical structure based on known mutagenic and carcinogenic structural analogy (Benfenati et al. 2019).

3 Result and discussion

3.1 Molecular docking studies

The main aim of the study was to prospect active chemical constituents of *Oroxylum indicum* to a highly conserved protein, M^{pro} of SARS-CoV-2, therefore we performed molecular docking studies of all chemical constituents of *Oroxylum indicum* followed by identification of top hits which is discussed below. Furthermore, to investigate pharmacokinetics and toxicity properties of the molecules showing promising results so that they can be proposed as potential drugs candidates.

Autodock Vina is used to determine molecular interactions and binding energy between phytoconstituents of *Oroxylum indicum* and COVID-19 M^{pro}. Phytoccosntituents

Table 1 Binding interactions of ligands with the binding site of main protease of SARS-CoV-2 (PDB ID: 6LU7)

Inhibitor	Binding Energy (kcal/mol)	Amino acids with hydrogen bonds	Amino acids with hydrophobic Interactions
1. Baicalein-7-*O*-diglucoside (10077207)	−9.1	GLY 143A, SER 144A, CYS 145A, HIS 163A, GLU 166A, ASP 187A, THR 190A, GLN 192A	MET 165A
2. Chrysin-7-*O*-glucuronide (14135335)	−8.6	THR 26 A, LEU 141 A, GLY 143A, SER 144A, CYS 145A	MET 165 A, GLN 189 A
3. Oroxindin (3084961)	−8.1	THR 26 A, ASN 142A,, GLY 143A, CYS 145A, ASP 187A	MET 165 A, GLN 189 A, PRO 168A
4. Scutellarein (5281697)	−8.0	TYR 54A, HIS 163A, HIS 164A, GLU 166A, ASP 187A	GLU 166A
5. N3 (4883311)	−8.0	GLY 143A, SER 144A, CYS 145A, HIS 163A, HIS 164A, GLU 166A, GLN 189A	THR 25A, HIS 41A, ASP 187A, GLN 189A
6. Remdesivir (121304016)	−7.9	ASN 142A, GLY 143A, SER 144A, CYS 145A, HIS 163A, GLU 166A, GLN 189A	THR 25A, MET 49A, MET 165A, GLU 166A, ASP 187A, GLN 189A

Table 2 Results of predicted toxicity of ligand with superior docking scores (pkCSM)

Sr. no.	ADMET properties	Baicalein-7-*O*-diglucoside	Chrysin-7-*O*-glucuronide	Oroxindin	Scutellarein
1	MW (g/mol)	594.5	430.4	460.4	286.24
2	log*P*	−1.3	1.5	1.4	1.4
3	HB Donor	9	5	5	4
4	HB Acceptor	15	10	11	6
5	AMES toxicity	No	No	No	No
6	Max tolerated dose (log mg/kg/day)	0.371	0.708	0.565	0.626
7	hERG I inhibitor	No	No	No	No
8	hERG II inhibitor	Yes	No	No	No
9	Acute oral rat toxicity, LD50 (mol/kg)	2.488	2.744	2.656	2.452
10	Chronic oral rat toxicity, LOAEL (log mg/kgbw/day)	5.125	4.574	4.003	3.135
11	Hepatotoxicity	No	No	No	No
12	skin sensitization	No	No	No	No
13	*T. pyriformis* (log µg/L)	0.285	0.285	0.285	0.301
14	Minnow toxicity (log mM)	10.29	4.297	4.005	1.99
15	Docking Score	−9.1	−8.6	−8.1	−8
16	Lipinski's rule violations	Yes	No	Yes	No

of *Oroxylum indicum* has shown antiviral actions (Mohamat et al. 2018; Antonio et al. 2020). Therefore we selected 18 chemical constituents from this plant to investigate their inhibition potential for COVID-19 M^{pro}. Remdesivir is shown potential in treatment of Marburg virus, Paramyxoviridae (such as parainfluenza type 3, Nipah, Hendra, measles and mumps viruses) and Pneumoviridae (respiratory syncytial virus) (Ko et al. 2020) that can represent possible treatment options against corona (Mahmood et al. 2020) it was selected as standard drug (Pizzorno et al. 2020).

The binding potential energy or Vina fitness score obtained from docking 6LU7 with the native ligand (N3) Fig S2, Remdesivir and *Oroxylum indicum* compounds are given in Table S1. The binding energy of the best docked pose of ligand is compared with co-crystalized ligand and reference standard drug. The docked binding energy of the N3 and Remdesivir is placed in the fifth and sixth position, a bit lower than those of the four best ligands. The binding affinity values range from −9.1 to −6.2 kcal/mol. There is no doubt that the Baicalein-7-*O*-diglucoside exhibits the higher

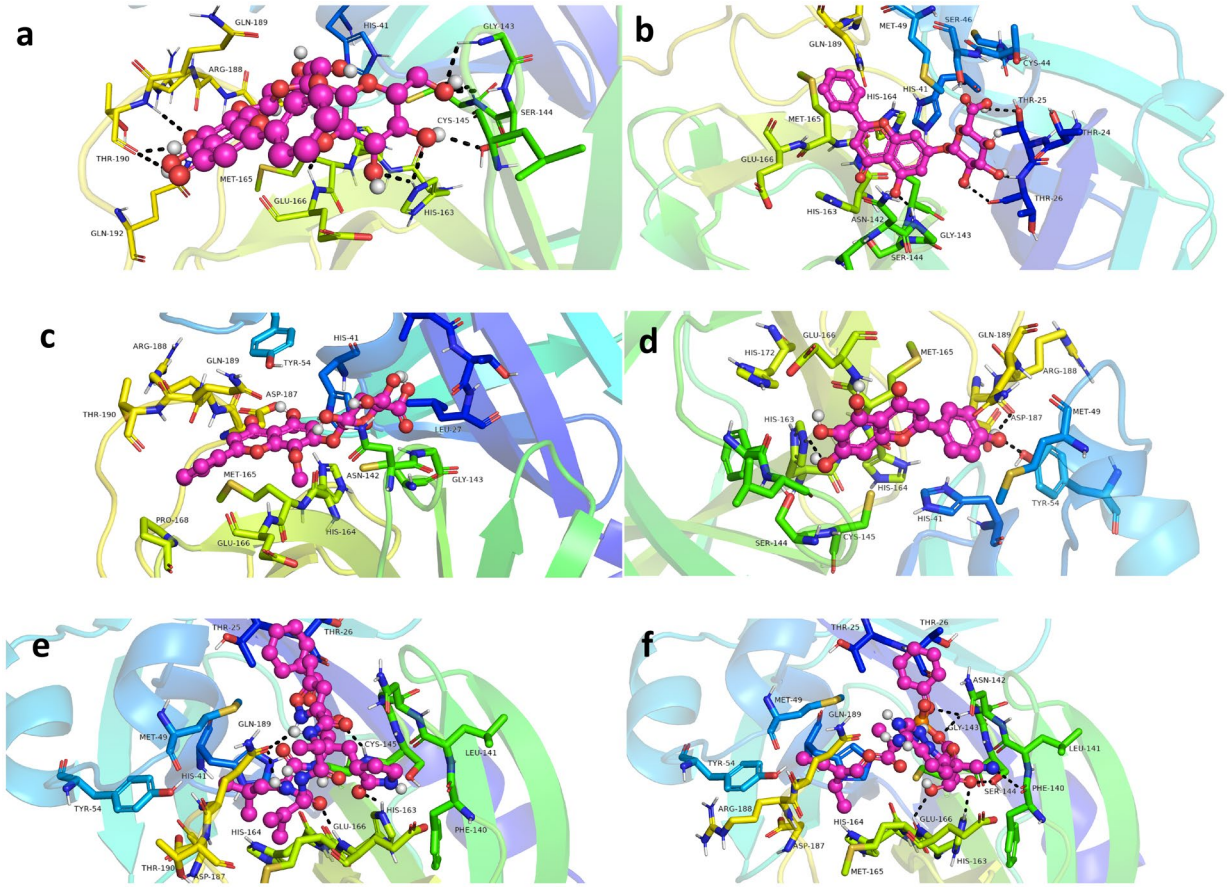

Fig. 2 Docked pose of **a** Baicalein-7-*O*-diglucoside **b** Chrysin-7-*O*-glucuronide and **c** Oroxindin, **d** Scutellarein, **e** N3, **f** Remdesivir against M^{pro} protease (PDB ID: 6LU7). The ligand is shown in ball and stick representation whereas residues forming binding pocket of M^{pro} are shown as colored sticks. Hydrogen bond interactions are shown with black dotted lines

binding affinity (−9.1 kcal/mol), higher to Chrysin-7-*O*-glucuronide (−8.6 kcal/mol), Oroxindin (−8.1 kcal/mol) and Scutellarein (−8.0 kcal/mol).

According to the analysis of docking results, the interactions (listed in Table 1) between Baicalein-7-*O*-diglucoside, Chrysin-7-*O*-glucuronide, Oroxindin and Scutellarein are highly consistent with that of Remdesivir and even they represent the most promising inhibitors of the SARS-CoV-2 M^{pro}. The results of the molecular docking showed that the tested compound baicalein-7-*O*-diglucoside gives the lowest binding energy (−9.1 kcal/mol) in complex with 6LU7, which is the best score when compared to other docked compounds. However, it is reasonably disapproving to obey Lipinski's rule of five as it is characterized by two violations (Table 2).

The docking of Chrysin-7-*O*-glucuronide with main protease is accompanied by an affinity of −8.6 kcal/mol by forming five hydrogen bonds with THR 26 A, LEU 141 A, GLY 143A, SER 144A, CYS 145A along with hydrophobic interaction with MET 165 A, GLN 189 A. It shows favorable drug-like properties by following Lipinski's rule of five without any violation. Both Oroxindin and Scutellarein exhibit drug-likeness as they were found to obey Lipinski's rule of five. Oroxindin was found to exhibit a hydrogen bond with THR 26 A, ASN 142A, GLY 143A, CYS 145A, ASP 187A and residue of the main protease with an affinity of −8.1 kcal/mol. It also forms pi–pi T-shape interactions with His 41A, pi-alkyl interactions with PRO 168A (Fig S3). Similarly, Scutellarein can be recognized as promising drug candidate on the basis of qualifying Lipinski's rule five. Scutellarein was found to show carbon-hydrogen bonding with TYR 54A, HIS 163A, HIS 164A, GLU 166A, ASP 187A and pi-alkyl interaction with MET 49A.

Hydrogen bonds formed by OH and C=O groups stabilizes ligand-receptor complex in which ligand plays dual role of acceptor and donor (Matondo et al. 2018) (Fig. 3 and Table 1). Also, stability of complexes are directed by dispersion forces (Trujillo and Sánchez-Sanz 2016), π–π interactions(Kasende et al. 2017), and hydrophobic interactions (Muya et al. 2019) types of interactions. It is the interaction (both lipophilic and H-bonds) between polar amino

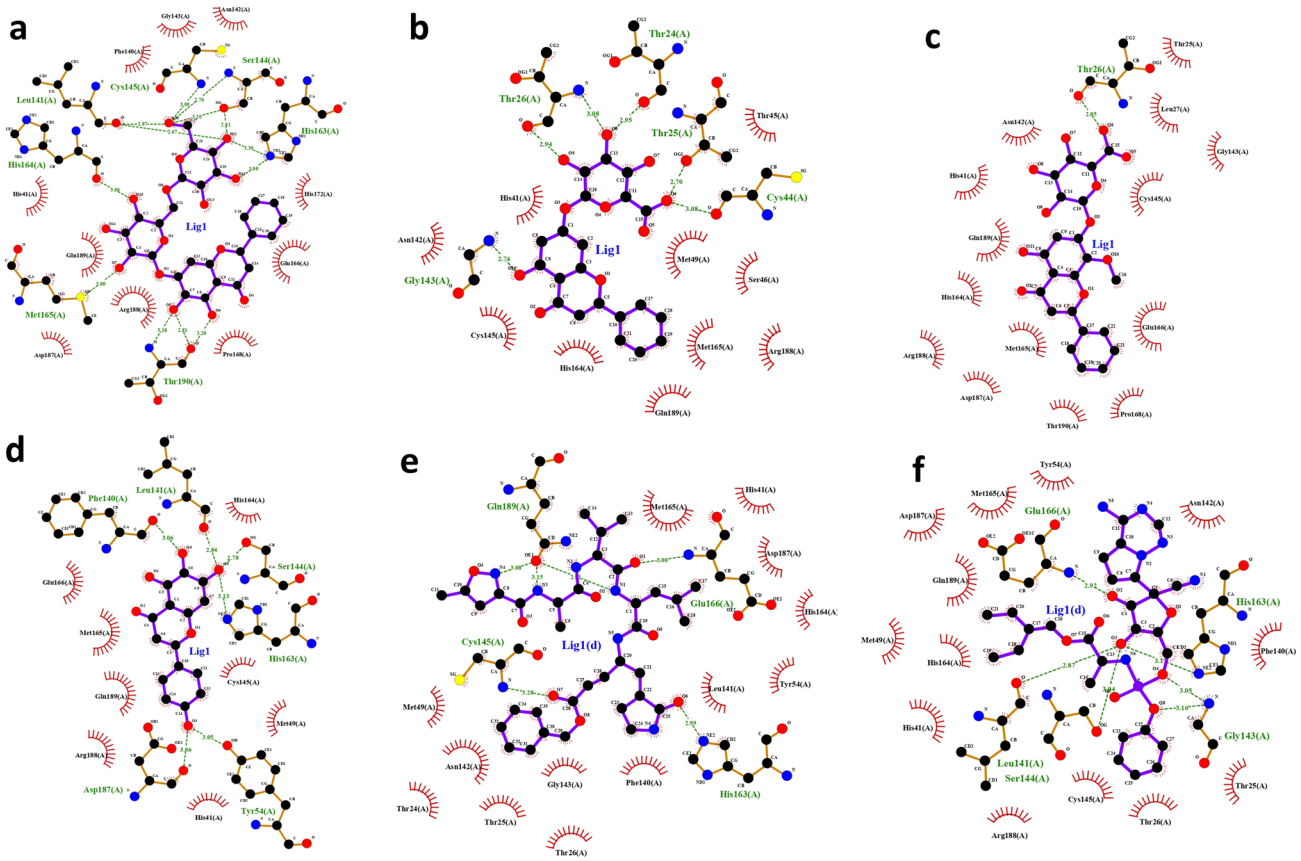

Fig. 3 Hydrogen-bonds parameters (distances and angles) **a** Baicalein-7-*O*-diglucoside, **b** Chrysin-7-*O*-glucuronide and **c** Oroxindin, **d** Scutellarein, **e** N3, **f** Remdesivir

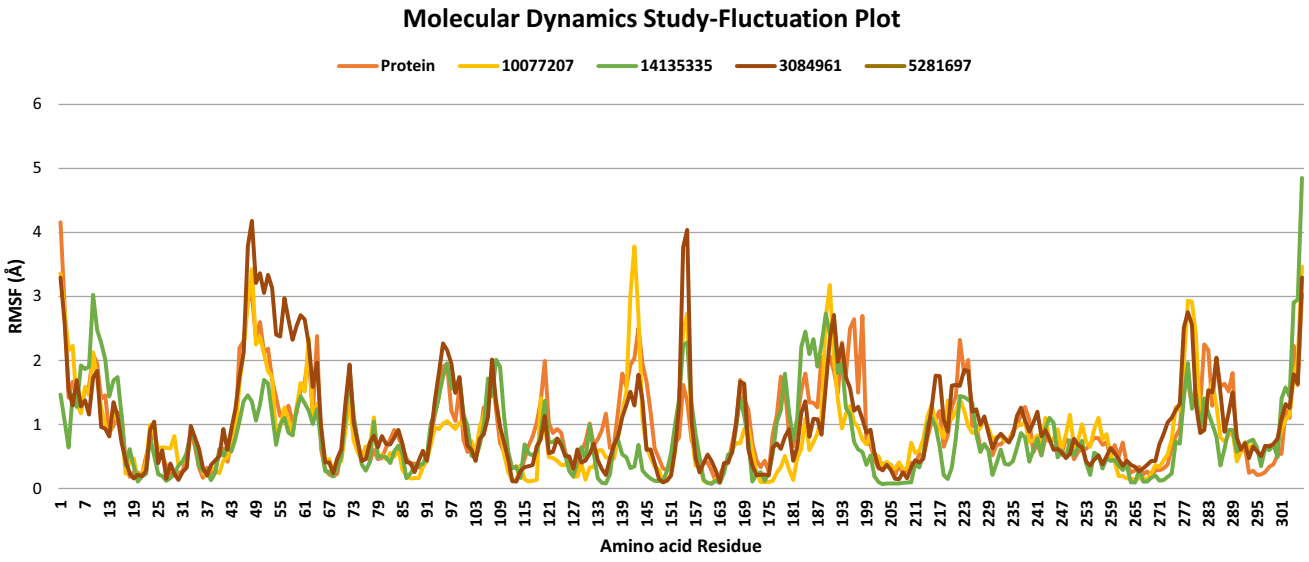

Fig. 4 Root Mean Square Fluctuations plots of protein structure with compounds. No abrupt fluctuations were observed in any region of the protein with the proposed ligands. **a** N3, **b** Baicalein-7-*O*-diglucoside (10077207), **c** Chrysin-7-*O*-glucuronide (14135335), **d** Oroxindin (3084961) and **e** Scutellarein (5281697)

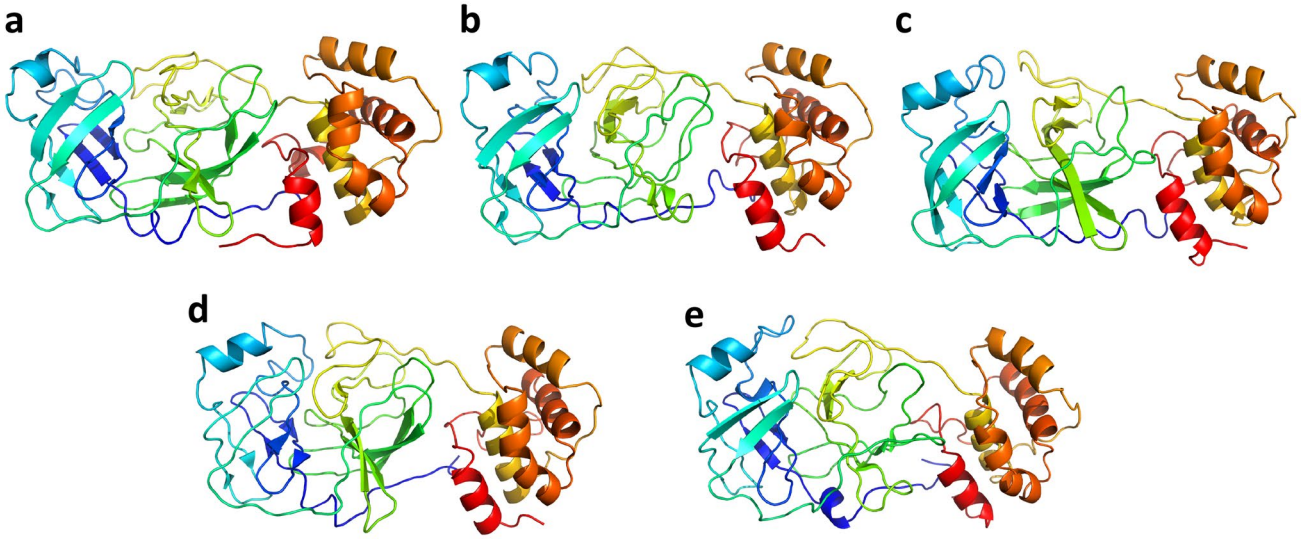

Fig. 5 Stable structures of protein generated after MD Simulation of compound. **a** N3, **b** Baicalein-7-*O*-diglucoside, **c** Chrysin-7-*O*-glucuronide, **d** Oroxindin and **e** Scutellarein

acid and hydrophobic residues are responsible to inhibit COVID-19 M^{pro} (Figs. 2, 3) (Khaerunnisa et al. 2020).

3.2 Molecular dynamics studies

Molecular dynamics studies are performed to validate docking results of phytoconstituents in complex with target protein 6LU7 using CABS-flex 2.0 server. The input of docking poses of phytoconstiutents complexed with protein (PDB) added with default parameters to study fluctuations of the individual amino acid residues (Jamroz et al. 2013). The conformational stability of docked poses are represented by the root mean square fluctuation (RMSF) values (Figs. 4, 5). The highest RMSF value in MD simulations reflects more flexibility of protein, whereas the lowest value implies the limited motion of the system during the simulation process (Zhao et al. 2015). Chrysin-7-*O*-glucuronide shows lowest RMSF values indicating limited motion of the system over period of simulation trajectories which also validates that Autodock Vina docking results are not obtained by chance. The presence of amino acid residues with fitting α-helix and β-sheet in secondary structures reflects minimal fluctuation with efficient constraints to the all atom. All the selected molecules (Baicalein-7-*O*-diglucoside, Chrysin-7-*O*-glucuronide, Oroxindin and Scutellarein) maintained the molecular interactions with the protein.

3.3 ADME and toxicity studies

The results of the pkCSM webserver shows that selected screened phytoconstituents does not have AMES toxicity, does not inhibit hERG-I, does not produce hepatotoxicity, it does not cause skin sensitivity. Only Baicalein-7-*O*-diglucoside inhibit hERG-II other do not. From the Lipinski and predicted ADME/tox filtering analyses (Table 2), we obtained four non-toxic, herbal compounds that bind to the receptor-binding site and catalytic site of SARS-CoV-2 M^{pro}.

Additionally to confirm reliability of toxicological data, QSAR modelling method performed using VEGA-QSAR (Table 3). The software incorporated algorithm provides evaluation of reliability prediction as Applicability domain index (ADI) value. We used positive results with ADI > 0.5, as indicators of reliability effect; low ($0.5 < ADI < 0.6$), medium ($0.6 < ADI < 0.8$) and high ($0.8 < ADI < 1$). The four phytoconstituents does not have AMES toxicity (CONSENSUS model, assessment and prediction) (Votano et al. 2004), does not have carcinogenicity (CAESAR model, assessment and prediction) (Fjodorova et al. 2010), no adverse health effects to humans and ecological species (IRFMN/COMPARA, assessment and prediction) (Kamel et al. 2020) and found to be inactive for Thyroid hormone receptor α/β (NRMEA, assessment and prediction). Unlike Scutellarine all compounds does not have skin sensitivity (CAESAR model, assessment and prediction) (Chaudhry et al. 2010). However, all compounds controversial to webserver predictions have very low reliability of hepatotoxic potential (IRFMN, assessment and prediction).

A literature review supports the docking result and reveals that extract of selected plant were reported to possess antimicrobial activities (Mat Ali et al. 1998; Suresh Babu et al. 2005) and act as antioxidant by inhibiting lipid-peroxidation (IC50 0.08 µg/ml) (Siriwatanametanon et al. 2010; Rajkumar et al. 2012). Baicalein extensively investigated with respect to their antiviral activity. It possess potent anti-DENV activity

Table 3 Toxicological data of selected active phytoconstituents (QSAR Models)

Sr. no.	Toxicity test	Remdesivir	Baicalein-7-*O*-diglucoside	Chrysin-7-*O*-glucuronide	Oroxindin	Scutellarein
1	Mutagenicity (Ames test) CONSENSUS model—assessment	0.1	0.5	0.25	0.25	0.5
	Mutagenicity (Ames test) CONSENSUS model—prediction	Mutagenic	NON-Mutagenic	NON-Mutagenic	NON-Mutagenic	NON-Mutagenic
2	Carcinogenicity model (CAESAR)—assessment	0.156*	0.61**	0.642**	0.633**	0.683**
	Carcinogenicity model (CAESAR)—prediction	NON-Carcinogen	NON-Carcinogen	NON-Carcinogen	NON-Carcinogen	NON-Carcinogen
3	Androgen Receptor-mediated effect (IRFMN/COMPARA)—assessment	0.612*	0.732**	0.5*	0.5*	0.693**
	Androgen Receptor-mediated effect (IRFMN/COMPARA)—prediction	NON-active	NON-active	NON-active	NON-active	Active
4	Thyroid Receptor Alpha effect (NRMEA)—assessment	0.866***	0.965***	0.922***	0.922***	0.942***
	Thyroid Receptor Alpha effect (NRMEA)—prediction	Inactive	Inactive	Inactive	Inactive	Inactive
5	Thyroid Receptor Beta effect (NRMEA)—assessment	0.866***	0.965***	0.922***	0.922***	0.942***
	Thyroid Receptor Beta effect (NRMEA)—prediction	Inactive	Inactive	Inactive	Inactive	Inactive
6	Skin Sensitization model (CAESAR)—assessment	0.5*	0.741*	0.5*	0.5*	0.615**
	Skin Sensitization model (CAESAR)—prediction	NON-Sensitizer	NON-Sensitizer	NON-Sensitizer	NON-Sensitizer	Sensitizer
7	Hepatotoxicity model (IRFMN)—assessment	0.5*	0.575*	0.543*	0.546*	0.779*
	Hepatotoxicity model (IRFMN)—prediction	Toxic	Toxic	Toxic	Toxic	Toxic

*Low reliability prediction; **medium reliability prediction; and ***high reliability prediction

(Moghaddam et al. 2014), impaired H5N1 virus replication, prolong death rate in individual infected with H1N1 and Sendai viruses, suppress replication of HIV-I virus. Computational studies also promises effectiveness against chikungunya virus (CHIKV) nsP3 and NS5 protein (Zakaryan et al. 2017). In vitro, scutellarein found to inhibit the SARS-CoV helicase protein by affecting the ATPase activity, nsP13 (Yu et al. 2012). Scutellarin and Chrysin-7-*O*-glucuronide showed high antioxidant capacities in DPPH, ABTS and CAA assays, antiviral activity of Chrysin derivative against Coxsackievirus B3 (CVB3) (Li et al. 2018).

Thus, we anticipate that this selected phytoconstituents has the potential to enhance immunity along with the inhibition of COVID-19 infections (Lin and Weng 2006). Furthermore, Combination therapy often results in superior outcome in antiviral treatments (Mucsi et al. 1992; Chang et al. 2011).

The screened phytoconstituents with antiviral activity, displayed higher docking scores, stronger binding energies, better interaction with the conserved catalytic residues and that may cause inhibition/blockade of the SARS-CoV-host protein pathways could be potential supportive and therapeutic candidates (Fuzimoto and Isidoro 2020).

4 Conclusion

Oroxylum indicum, a medicinal plant traditionally uses as antiviral, contains chemical constituents which has potential for prevention and prophylaxis of SARS-CoV-2. Computational algorithmic screening of the selected phytoconstituents of the plant were highly selective, shown strong binding potential and have strong interactions with main protease M^{pro} of SARS-CoV-2 virus. The evidence of highest docking score, positioning of ligands at site of inhibition, interaction profile with catalytic residues and acceptable ADMET parameters by QSAR model suggest probability of Chrysin-7-*O*-glucuronide may be potent against SARS-CoV-2 M^{pro}. These results encourage further in vitro and in vivo investigations and also encourage traditional use of *Oroxylum indicum* preventively and will provide vital information on novel scaffolds for further lead optimization.

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Authors and Affiliations

Sapan Shah[1] · Dinesh Chaple[1] · Sumit Arora[2] · Subhash Yende[3] · Keshav Moharir[4] · Govind Lohiya[4]

Dinesh Chaple
d.chaple@rediffmail.com

Sumit Arora
sumitkishanarora@gmail.com

Subhash Yende
subhashyende@gmail.com

Keshav Moharir
keshavmoharir@gmail.com

Govind Lohiya
lohiyagovind@gmail.com

[1] Department of Pharmaceutical Chemistry, Priyadarshini J. L. College of Pharmacy, Hingna Road, Nagpur, Maharashtra 440016, India

[2] Pharmacognosy and Phytochemistry Division, Gurunanak College of Pharmacy, Nari, Nagpur, Maharashtra 440026, India

[3] Pharmacology Department, Gurunanak College of Pharmacy, Nari, Nagpur, Maharashtra 440026, India

[4] Pharmaceutics Department, Gurunanak College of Pharmacy, Nari, Nagpur, Maharashtra 440026, India